Dynamic changes in replication timing and gene expression during lineage specification of human pluripotent stem cells.

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Public Summary:
We analyzed changes in gene expression as hESCs differentiated along several different lineages. Analysis of transcriptional regulatory networks showed that this class of genes contains strong regulators of genes that were only expressed when early replicating. These results provide intriguing new insight into the complex relationship between transcription and replication-timing regulation during human development.

Scientific Abstract:
Duplication of the genome in mammalian cells occurs in a defined temporal order referred to as its replication-timing (RT) program. RT changes dynamically during development, regulated in units of 400-800 kb referred to as replication domains (RDs). Changes in RT are generally coordinated with transcriptional competence and changes in subnuclear position. We generated genome-wide RT profiles for 26 distinct human cell types, including embryonic stem cell (hESC)-derived, primary cells and established cell lines representing intermediate stages of endoderm, mesoderm, ectoderm, and neural crest (NC) development. We identified clusters of RDs that replicate at unique times in each stage (RT signatures) and confirmed global consolidation of the genome into larger synchronously replicating segments during differentiation. Surprisingly, transcriptome data revealed that the well-accepted correlation between early replication and transcriptional activity was restricted to RT-constitutive genes, whereas two-thirds of the genes that switched RT during differentiation were strongly expressed when late replicating in one or more cell types. Closer inspection revealed that transcription of this class of genes was frequently restricted to the lineage in which the RT switch occurred, but was induced prior to a late-to-early RT switch and/or down-regulated after an early-to-late RT switch. Analysis of transcriptional regulatory networks showed that this class of genes contains strong regulators of genes that were only expressed when early replicating. These results provide intriguing new insight into the complex relationship between transcription and RT regulation during human development.